Remarks

Claims 1-23, 28, 31, 35-36 and 44-50 were previously cancelled. Claims 26-27, 29, 32-33-34 are canceled herein. Claim 24 and 43 are amended herein to incorporate the limitations of claims 34. Additional support for the amendment of claim 24 and 43 can be found throughout the specification, such as, but not limited to, page 1, lines 11-15, page 2, lines 30 to page 3, line 26l and page 29, line 14 to page 32, line 25; page 36, lines 6-22, and in the Examples section. New claim 53 is added herein. Claims 37 and 38 are amended to correct form.

Reconsideration of the application is respectfully requested in view of the foregoing amendments and following remarks. Applicants believe no new matter is added herein.

Objections to the Specification

The specification is objected to for including use of trademarks, such as on pages 30-31. The specification is amended herein to capitalize trademarks (which are accompanied by the generic terminology) rendering the objection moot.

Double Patenting

Claims 24-27, 29-30, 32-34, 37-39, 43 and 51-52 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 22-25, 27 and 68-75 of co-pending Application No. 10/489,839. Submitted herewith is a terminal disclaimer, disclaiming the terminal portion of any patent issued from the above-referenced application that would extend beyond the term of any patent that issues from U.S. Application No. 10/489,839. The submission of this terminal disclaimer renders the rejection moot.

Claim Rejections – 35 USC § 112

The Action rejects claims 24-27, 29-30, 32-34, 37-43 and 51-52 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. Applicants respectfully disagree with this rejection as applied to the claims as amended.

Nature of the Invention: The claims are directed to methods of suppressing an immune response in an inflammatory arthropathy in a subject using an oligodeoxynucleotide comprising SEQ ID NO: 2.

Breadth of the Claims: The claims as amended are limited to the suppression of an immune response only in an inflammatory arthropathy, and are limited to the use of oligodexoynucleotides (ODNs) including a very specific nucleotide sequence, namely SEQ ID NO: 2.

State of the Art: Applicants agree that the prior art teaches that both LPS and ODNs with a CpG motif induce arthirits. In addition, the synthesis of ODNs is routine.

Level of Skill of One in the Art: The level of skill of one in the art, such a molecular biologist or rheumatologist is high.

Guidance in the Specification: The Office action alleges that the specification "fails to disclose the correlation between treatment of inflammatory arthropathy and suppression of CpG-induced inflammation." This is incorrect.

As noted in the Office action, Gursel et al. (*J. Immunol.* 171: 1393-1400, 2003, published after the filing date of the parent PCT application) disclose that ODNs with TTAGGG motifs down-regulate the response to immunostimulatory DNA including CpG motifs. These suppressive ODNs block co-localization of CpG DNA with TLR9 in endosomal vesicles. Thus, Gursel et al. disclose that suppressive ODNs of 10 to 30 nucleotides in length that form a G-tetrad, have more than two guanosines, and have a CD value of greater than 2.9, such as SEQ ID NO: 2 can be used to suppress an immune response.

Gursel et al. describe that suppressive ODNs suppress IL-12 production (see Fig. 1). Suppressive ODNs also "inhibit a broad range of immune stimulation in a dose dependent fashion, including up-regulation of costimulatory molecules on APCs, IgM production by B cells, and NO release from macrophages ($p< 0.001$; Fig. 3a and Table I)" (see page 1395, second column). Gursel et al. confirm that G-tetrad formation and the CD value are critical for immunosuppressive activity. Thus, Gursel et al. confirm that an ODN comprising SEQ ID NO: 2 have all the features of a suppressive ODN.

Gursel et al. does disclose that suppressive ODNs do not significantly reduce LPS induced cytokine production. LPS is a key agent in the induction of toxic shock syndrome, and joint pain is one symptom of toxic shock syndrome. Thus, Gursel et al. could be construed to

disclose that suppressive ODNs are not of use for treating toxic shock. However, the claims are not directed to methods of treating toxic shock, or reducing an immune response to LPS; the claims are directed to suppressing an immune response in inflammatory arthritis. Thus, the lack of an effect of suppressive ODNs on LPS-induced inflammation is not relevant.

Gursel et al. does disclose that suppressive ODN block the co-localization of CpG ODNs with TLR9. However, this does not negate the effectiveness of suppressive ODNs on the reduction of inflammatory arthritis noted in animal models (see below).

Moreover, Example 5 of the present specification document the effect of an ODN comprising SEQ ID NO: 2. Specifically, this example discloses that suppressive ODN including SEQ ID NO: 2 were administered to mice with inflammatory arthritis induced by collagen. Treatment significantly reduced both the percentage of mice that developed arthritis and the arthritis clinical score. The production of anti-collagen antibodies (an immune response) was suppressed by treatment with an ODN comprising SEQ ID NO: 2. Local expression of pro-inflammatory cytokines was also suppressed.

Submitted herewith as Exhibit A is Dong et al., Arthritis & Rheumatism 50: 1686-1689, 2004, which presents additional confirmatory data showing that ODNs comprising SEQ ID NO: 2 (such as A151) decreased serum titers of pathogenic anti-collagen II antibodies and interferon gamma by T cells in collagen-induced inflammatory arthritis in mice. Dong et al. confirms that the beneficial effect of administering suppressive ODN (specifically an ODN comprising SEQ ID NO: 2) are associated with the inhibition of cellular and humoral immune response (see page 1686, second column).

In the collagen-induced arthritis model there is no administration of CpG ODNs. Thus, with regard to this model system, suppressive ODNs cannot affect the co-localization of CpG ODNs with TLR9, yet inflammatory arthritis is still inhibited in the animals. Thus, the finding of Guersel et al. that suppressive ODNs effect co-localization of CpG ODNs with TLR9 cannot be construed to negate the utility of suppressive ODNs for the treatment of inflammatory arthritis.

Thus, there is clear documentation that the administration of suppressive ODNs comprising SEQ ID NO: 2 can be used to suppress an immune response in inflammatory arthritis in a subject.

Working Examples: Evidence in several animal models has been presented to document that suppressive ODNs can be used to treat inflammatory arthritis. An ODN comprising SEQ ID NO: 2 was able to suppress immune responses in a mouse model of an inflammatory arthropathy, as shown in Example 5. Additional data from this mouse model, documenting the suppression of an immune response in inflammatory arthropathy in a subject is presented in Exhibit A.

Specifically, the Office action states that "no example demonstrates the state of inflammatory arthropathy in the subjects." This is clearly incorrect, as data is presented in animal models of arthritis in Examples 5 and Exhibit A. The administration of a suppressive ODN comprising SEQ ID NO: 2 is correlated to arthritis incidence and clinical score (a measure of joint swelling, joint rigidity and bony deformity). In these examples, the state of inflammatory arthropathy is related to the administration of suppressive ODNs and to the induction of an immune response. In the results presented in Exhibit A (and Example 5), the effect of the ODNs on specific parameters of the immune system (lymphocyte infiltration into the joints, cytokine secretion and antibody secretion) is correlated with the effect of suppressive ODNs.

Predictability in the art: The Office action asserts that "there is no way one could predict this method in any aspect given the lack of crucial support in the specification." Applicants respectfully disagree. This statement in the Office action is simply a broad generalization; no specific deficiencies are noted.

One of skill in the art can readily produce suppressive ODNs comprising SEQ ID NO: 2. In addition, the specification described results obtained in a mouse model documenting the use of an ODN comprising SEQ ID NO: 2 to suppress an immune response in a subject with an inflammatory arthropathy. Exhibit A presents additional confirmatory data showing that synthetic ODNs comprising SEQ ID NO: 2 decrease serum titers of pathogenic anti-collagen II antibodies and interferon gamma by T cells in a mouse model of an inflammatory arthropathy. Thus, the data provided in the specification, as well as the additional work presented in Exhibit A, documents the predictability of the claimed methods.

Amount of experimentation necessary: The Office action alleges that too much experimentation is required to use any suppressive ODN. Applicants respectfully disagree. However, solely to advance prosecution, the claims are now limited to the use of ODNs comprising SEQ ID NO: 2. One of skill in the art can readily produce ODNs comprising this exact nucleic acid sequence.

The Office action further alleges that undue experimentation is required due to the "lack of a proper model for the successful treatment of inflammatory arthropathy." Applicants respectfully disagree with this rejection. Results are presented in the specification using art-recognized animal models (see example 5 and Dong et al, Exhibit A). Dong et al. (Exhibit A) states "collagen induced arthritis (CIA) is a well-established murine model of RA [rheumatoid arthritis] that has helped in the examination of poteintial treatments and in the clarification of the pathogenesis of disease" (see page 1686, first column). MPEP 2107.02 states:

> As a general matter, evidence of pharmacological or other biological activity of a compound will be relevant to an asserted therapeutic use if there is *a reasonable correlation between the activity in question and the asserted utility.* Cross v. Iizuka, 753 F.2d 1040, 224 USPQ 739 (Fed. Cir. 1985); In re Jolles, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); Nelson v. Bowler, 626 F.2d 853, 206 USPQ 881 (CCPA 1980). An applicant can establish this reasonable correlation by relying on statistically relevant data documenting the activity of a compound or composition, arguments or reasoning, documentary evidence (e.g., articles in scientific journals), or any combination thereof. The applicant does not have to prove that a correlation exists between a particular activity and an asserted therapeutic use of a compound as a matter of statistical certainty, nor does he or she have to provide actual evidence of success in treating humans where such a utility is asserted. Instead, as the courts have repeatedly held, *all that is required is a reasonable correlation between the activity and the asserted use* Nelson v. Bowler, 626 F.2d 853, 857, 206 USPQ 881, 884 (CCPA 1980). [emphasis added]

MPEP 2164.02 describes the use of animal models to support a claimed utility. Although these sections are directed to the use of claimed compounds and methods, Applicants believe that they are also relevant to the present enablement rejection. MPEP 2164.02 states:

> The issue of "correlation" is related to the issue of the presence or absence of working examples. "Correlation" as used herein refers to the relationship between *in vitro* or *in vivo* animal model assays and a disclosed or a claimed method of use. An *in vitro* or *in vivo* animal model example in the specification, in effect, constitutes a "working example" if that example "correlates" with a disclosed or

> claimed method invention.... In other words, *if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating* unless the examiner has evidence that the model does not correlate....A rigorous or an invariable exact correlation is not required, as stated in *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985):
>
> [B]ased upon the relevant evidence as a whole, there is a reasonable correlation between the disclosed *in vitro* utility and an *in vivo* activity, and therefore a rigorous correlation is not necessary where the disclosure of pharmacological activity is reasonable based upon the probative evidence. (Citations omitted.)

The documentation of the effect of suppressive ODNs comprising SEQ ID NO: 2 in an art-recognized animal model documents that only limited experimentation would be required.

Applicants submit that the claimed methods are fully enabled by the specification. Reconsideration and withdrawal of the rejection are respectfully requested.

Conclusion and Renewed Request for an Interview

Applicants believe the present application is ready for allowance, which action is requested. This request is being submitted under MPEP § 713.01, which indicates that an interview may be arranged in advance by a written request. If any issues remain prior to the issuance of a Notice of Allowance, applicants respectfully request that Examiner Horning and/or Examiner Campell contact the undersigned at the telephone number listed below.

Respectfully submitted,

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